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Knife or Needles? A Cohort Analysis of Outcomes after Radical Prostatectomy or Brachytherapy for Men with Low- or Intermediate-Risk Adenocarcinoma of the Prostate

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Prostate cancer; prostate surgery; comparative effectiveness; Gleason Score; interstitial implant; seeds; prostate biopsy; LDR brachytherapy

INTRODUCTION

Men with clinically localized prostate cancer face several treatment options, including active surveillance, external beam radiation, radical prostatectomy (RP), and brachytherapy (BT). The choice of the best treatment for an individual patient can be difficult because few randomized clinical trials provide data that directly compares the outcomes after these treatment modalities.. One randomized clinical trial compared biochemical recurrence–free survival (BRFS) after BT or RP by randomizing 200 men with low-risk prostate cancer to interstitial or surgical therapy. That trial demonstrated no difference in 5-year BRFS rates between BT (92%) and RP (91%). [1] Another trial, SPIRIT, was initiated to compare BT and RP for treating favorable-risk disease, but accrual was slow and no mature data have been produced. [2] No other randomized data directly comparing BT to RP exist at this time.

Retrospective analyses of outcomes after long-term follow-up indicate that BT produces results similar to those after RP or external beam radiation therapy, [3,4] although BRFS results are more mixed among men with intermediate-risk prostate cancer. D’Amico and colleagues reported that BT produced inferior survival for intermediate-risk disease

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compared with RP or external beam therapy, [5] but others have reported equivalent outcomes after BT or other modalities for intermediate-risk disease. [6,7]

One potential advantage of surgery over radiation therapy is the ability to analyze the entire prostate, with the goal of identifying pathologic features that could influence the choice of adjuvant therapy. Bostwick and colleagues noted that the accuracy of Gleason score (GS) assessment tends to be lower for low-grade or small-volume tumors, which constitute a significant percentage of cases diagnosed in the prostate-specific antigen (PSA) era. [8] The rate at which GS, and thus disease, is upgraded between biopsy and RP specimens varies widely, with some institutions reporting discordance in up to 70% of cases. [9] One report from the Mayo Clinic found that GS assigned at biopsy had a minimal effect on predicting cancer-specific mortality in their cohort, [10] but this has not been systematically examined elsewhere.

Because patients treated with BT undergo the same biopsy procedure and disease staging process as those who undergo RP, logically the extent of pathologic upgrading would be similar for such men if their prostates were removed. Comparing the outcomes among men who undergo BT and men who undergo RP based on both their biopsy grade as well as the RP grade would allow the impact of upgrading on outcome to be assessed. Attempts to identify which cases will be upgraded have revealed several possible risk factors, including the number of biopsy cores obtained (cases in which multiple cores are obtained are much less likely to be upgraded), treatment at low-volume centers, prolonged intervals between biopsy and RP, and increasing PSA levels. King and others, addressing the implications of upgrading specifically for patients undergoing radiation therapy, noted that even the best nomograms cannot identify the risk of occult high-grade disease in patients undergoing radiation therapy. [11] Other potential risk factors for upgrading include a high percentage of positive biopsy cores, [12] prostate volume ($<75 \text{ cm}^3$), and high PSA levels ($>20 \text{ ng/mL}$). [13]

The purpose of this study was threefold: first, to compare outcomes (BRFS and prostate cancer-specific survival [PCSS]) for men with low- to intermediate-risk prostate cancer treated with BT or RP at a single tertiary care center; two, to assess the differences in GS from the biopsy specimen as assessed by the contributing pathologists, from the biopsy GS after central pathologic review, and from the RP specimen; and three, to determine if upgrading of GS influenced outcome.

METHODS

Patients

Patients were a subset of a large institutional database of clinical records linked with annotated pathology specimens from men with prostate cancer. The subset studied here consisted of 371 men with low- to intermediate-risk prostate cancer (GS 6–7, PSA level $< 20 \text{ ng/mL}$, and clinical stage T1a–T2c) who were treated with RP (n=279) or BT (n=92) from January 1, 2000 through December 31, 2001, at The University of Texas MD Anderson Cancer Center. All patients had undergone prostate biopsy at facilities other than MD Anderson Cancer Center and had specimens available for central pathology review. A protocol to retrospectively review these patient records was approved by the appropriate MD Anderson institutional review board.

Disease Staging

All of the men in this study had had a history and physical examination, including clinical staging by digital rectal examination (DRE), and pathologic confirmation of prostate cancer by transrectal ultrasound-guided prostate biopsy and pathology review at MD Anderson. All

biopsy specimens were reviewed by experienced pathologists specializing in genitourinary pathology. Men who had PSA levels exceeding 20 ng/mL, GS 8–10 disease, or clinical T3 or higher disease on presentation were excluded from this analysis.

Treatment

BT with iodine-125–loaded needles was performed while the patient was under general anesthesia, with ultrasound guidance used for prostate localization and treatment planning. The prescribed dose to the planning target volume was 145 Gy, and no patient in the BT group received external beam radiation therapy. CT-based dosimetry was assessed at Day 0 and Day 30 after implantation, and the treatment plans were evaluated at periodic genitourinary radiation oncology quality assurance meetings. Surgical therapy consisted of a radical retropubic prostatectomy, and no patient in the surgery group received external beam radiation therapy.

Follow-up

Follow-up visits generally occurred every 6 months until four years and then annually thereafter. The evaluation consisted of interim history and physical examinations, including DRE, and serum PSA measurements. Biochemical failure for the men undergoing BT was defined as nadir PSA level plus 2 ng/mL and for the men undergoing RP as a PSA level 0.4 ng/mL. The median follow-up time was 7.6 years for the BT group [range, 0.1–9.5 years] and 7.2 years [range, 0.0–9.1 years] for the RP group.

Statistical Methods

We used the product-limit estimator of Kaplan and Meier to estimate BRFS (median time and 5-year rate) and PCSS (median time and 5-year rate) for the RP vs. BT groups. Differences between the Kaplan-Meier curves were assessed with log-rank tests. We similarly compared BRFS and PCSS among men in each treatment group whose disease had been upgraded (or downgraded) after central pathologic review. All statistical analyses were performed using SAS 9.1 (2003) for Windows (SAS Institute, Cary NC).

RESULTS

Pretreatment characteristics of patients in both treatment groups are shown in Table 1. The RP patients were younger than those in the BT group (mean ages 60.1 years vs. 65.1 years, $p < 0.0001$). The two groups did not differ in terms of mean PSA level at presentation, 6.1 ng/mL for RP and 6.6 ng/mL for BT, or clinical disease stage. The majority of patients in both groups presented with cT1c or cT2a disease. Twenty-three (25%) BT patients had cyoreduction hormone therapy. The mean D90 was 153 Gy, and the median PSA for the 82 patients with a minimum PSA follow-up of 4 years was 0.05 with a mean of 0.41 (range 0.00 to 5.80). Of the men who underwent RP, 185 (66.3%) had biopsy GS 6 disease and 94 (33.7%) had GS 7 disease after central review, and for BT, 82 (89.1%) had GS 6 and 10 (10.9%) had GS 7 ($p < 0.0001$). Of the GS 7 patients in the RP group, 20 (21.3%) had (4+3) disease.

The pathology upgrading for patients in both groups is shown in Table 2. The GS from the biopsy specimen was upgraded (from GS 6 to GS 7) after central pathologic review in 36 men treated with RP (12.9%) and in 15 men treated with BT (16.3%) ($p = 0.18$). Of the 279 men treated with RP, the GS was upgraded from the centrally reviewed biopsy to the RP specimen in 121 (43.4%). The GS after RP was higher than the GS that had been assigned by the contributing pathologist in 144 men (51.6%). 48.3% of the patients with extended core biopsies had GS upgraded following RP.

The 5 year time to recurrence, BRFs, and PCSS for the RP group based on the biopsy GS 6 and 7 with central pathology review was 96.1% vs. 92.3% ($p=0.0201$), 94.4% vs 91.3% ($p=0.0865$), and 99.4% vs. 100%, respectively. In the RP group, the BRFs rates at 5 years were 92.5% for men with concordant GS (outside biopsy GS vs. MD Anderson central-review GS) and 97.2% for men with disease that was upgraded from GS 6 to GS 7 ($p=0.84$). However, the 5-year BRFs for low and intermediate risk RP patients was 96.1% and 90.6%, respectively ($p=0.003$). In the BT group, the 5-year BRFs rates were 91.6% for men with concordant GS and 100% in men with disease that was upgraded from GS 6 to GS 7 ($p=0.53$). The 5-year BRFs for low and intermediate risk BT patients was 92.5% and 95.8%, respectively ($p=0.017$). The Kaplan-Meier estimates of BRFs are illustrated in Figures 1 and 2.

Finally, we assessed whether the upgrading of GS from the centrally reviewed biopsy to the RP specimen influenced PCSS rates. Regardless of the treatment group, the 5-year PCSS in patients with upgraded GS to 7, either (3+4) or (4+3), was 100%.

DISCUSSION

This study is one of the first to evaluate and compare the long-term outcomes after RP or BT for men with low- to intermediate-risk prostate cancer after central pathologic review at a single tertiary care center. Our results from this cohort analysis showed that (1) outcomes in terms of BRFs and PCSS were equivalent after RP and BT for low- to intermediate-risk prostate cancer, (2) substantial upgrading was noted between biopsy and RP, even when both specimens had been read by genitourinary pathologists, and (3) upgrading did not influence outcomes in this population. While there is no reason why the pathologic upgrading rate among men treated primarily with radiation therapy should be lower than that observed among men undergoing RP in this study, information on upgrading from biopsy to whole-prostate specimens is not available for men treated primarily with BT. Therefore, one could assume that occult foci of higher-GS disease are likely present in such men, as was the case in 43.4% of the men who underwent RP in our study and thus the rate of upgrading after surgery may serve as a reasonable surrogate for pathology evaluation in patients treated with BT at MD Anderson.

The results of this study are significant with respect to clinical treatment recommendations, disease outcomes, and patient's quality of life. In the current PSA screening era, most men presenting to MD Anderson have a PSA level < 10 and clinical T1c-T2 localized disease, and the GS has become the basis of risk stratification and subsequent choice of treatment. Guidelines from the National Comprehensive Cancer Network (NCCN) indicate that patients with localized disease should be stratified according to GS into low-, intermediate-, and high-risk groups, which can significantly alter treatment recommendations and subsequent quality of life.[14] For example, for patients presenting with low-risk disease (GS 6), a monotherapy approach with BT is currently one standard-of-care option. However, having a biopsy grade of GS 7 indicates intermediate-risk disease, and the recommended treatment would include supplemental external beam radiation therapy with BT as well as 4–6 months of androgen deprivation therapy. The NCCN guidelines further suggest that patients with intermediate-risk disease should consider pelvic lymph node irradiation.[14] Finally, patients with high-risk localized prostate cancer (GS 8) are generally not considered optimal candidates for BT as monotherapy. Therefore, pathologic evaluation of the biopsy specimen is crucial in the decision-making process for patients with prostate cancer. The results of the current study suggest that outcomes after BT or RP as monotherapy are excellent even for patients whose GS scores were upgraded from 6 to 7, and therefore, additional therapy may not be warranted in such cases.

For more than half of the men in this study (51.6%), the GS assigned by the referring pathologist was lower than the final GS in the RP specimen. Our results agree with reports from other institutions citing significant rates of upgrading between biopsy GS and RP GS. [15,16] This phenomenon is largely attributed to the sampling limitations associated with biopsy versus the full prostatectomy specimen. Within this small cohort of patients with extended core biopsies (29 of 279 patients), we could not demonstrate a decrease in GS upgrading following RP.

The rate of upgrading between GS assigned at an outside institution and that assigned at MD Anderson was comparable between the two treatment groups (16.3% for BT patients and 12.9% for RP patients). Although Karakiewicz reported that upgrading in GS from biopsy to RP is more common at centers with lower patient volumes than at tertiary care centers,[17] we found substantial upgrading even when specimens were reviewed by the same group of pathologists, all of whom specialized in genitourinary cancer.

Our study had several notable limitations; first, it was retrospective in nature and subject to all of the inherent biases of such studies. Second, the number of biopsy cores obtained varied throughout the study period. Data from prospective randomized studies are mixed at present as to whether obtaining more cores will increase rates of cancer detection, but this practice could lead to differences in cancer detection rates among studies. [18,19] Finally only a modest number of men with intermediate-risk disease (GS 7) were treated with BT as monotherapy in this study (n=10). Nevertheless, if the findings on occult foci of higher-grade cancer from the surgical group are any indication, one might expect that disease in approximately 45% of men in the BT group would have been upgraded, which may have led in turn to changes in risk-group stratification and treatment recommendations. At MD Anderson, two prospective trials are currently underway to investigate the role of BT as monotherapy for patients presenting with intermediate-risk, localized disease. Outcome measures include disease outcomes and quality of life.

CONCLUSIONS

In conclusion, outcomes after RP and BT are excellent for men presenting with early-stage localized prostate cancer. Although a considerable proportion of biopsy specimens may be upgraded upon referral of such patients to a tertiary care center, caution should be exercised with regard to intensifying the treatment regimen, because upgrading may not influence patient outcomes.

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Abbreviations

RP	Radical Prostatectomy
BT	Brachytherapy
PSA	Prostate Specific Antigen
BRFS	Biochemical recurrence free survival
PCSS	Prostate Cancer Specific Survival
GS	Gleason Score

LDR	Low dose rate
DRE	Digital Rectal Examination

References

1. Giberti C, Chiono L, Gallo F, et al. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol.* 2009; 27:607–612. [PubMed: 19455340]
2. Wallace K, Fleshner N, Jewett M, et al. Impact of a multi-disciplinary patient education session on accrual to a difficult clinical trial: the Toronto experience with the surgical prostatectomy versus interstitial radiation intervention trial. *J Clin Oncol.* 2006; 24:4158–4162. [PubMed: 16943531]
3. Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol.* 2005; 173:1562–1566. [PubMed: 15821486]
4. Merrick GS, Butler WM, Lief JH, et al. Is brachytherapy comparable with radical prostatectomy and external-beam radiation for clinically localized prostate cancer? *Tech Urol.* 2001; 7:12–19. [PubMed: 11272667]
5. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA.* 1998; 280:969–974. [PubMed: 9749478]
6. Morris WJ, Keyes M, Palma D, et al. Population-based study of biochemical and survival outcomes after permanent 125I brachytherapy for low- and intermediate-risk prostate cancer. *Urology.* 2009; 73:860–865. discussion 865–867. [PubMed: 19168203]
7. Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy ≥ 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys.* 2004; 58:25–33. [PubMed: 14697417]
8. Bostwick DG. Gleason grading of prostatic needle biopsies. Correlation with grade in 316 matched prostatectomies. *Am J Surg Pathol.* 1994; 18:796–803. [PubMed: 8037294]
9. Noguchi M, Stamey TA, McNeal JE, et al. Relationship between systematic biopsies and histological features of 222 radical prostatectomy specimens: lack of prediction of tumor significance for men with nonpalpable prostate cancer. *J Urol.* 2001; 166:104–109. discussion 109–110. [PubMed: 11435833]
10. Boorjian SA, Karnes RJ, Crispen PL, et al. The impact of discordance between biopsy and pathological Gleason scores on survival after radical prostatectomy. *J Urol.* 2009; 181:95–104. discussion 104. [PubMed: 19012937]
11. King CR, McNeal JE, Gill H, et al. Extended prostate biopsy scheme improves reliability of Gleason grading: implications for radiotherapy patients. *Int J Radiat Oncol Biol Phys.* 2004; 59:386–391. [PubMed: 15145152]
12. Lee AK, Schultz D, Renshaw AA, et al. Optimizing patient selection for prostate monotherapy. *Int J Radiat Oncol Biol Phys.* 2001; 49:673–677. [PubMed: 11172948]
13. D'Amico AV, Renshaw AA, Arsenault L, et al. Clinical predictors of upgrading to Gleason grade 4 or 5 disease at radical prostatectomy: potential implications for patient selection for radiation and androgen suppression therapy. *Int J Radiat Oncol Biol Phys.* 1999; 45:841–846. [PubMed: 10571187]
14. NCCN. [Accessed January 22, 2012] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prostate Cancer. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf
15. Kulkarni GS, Lockwood G, Evans A, et al. Clinical predictors of Gleason score upgrading: implications for patients considering watchful waiting, active surveillance, or brachytherapy. *Cancer.* 2007; 109:2432–2438. [PubMed: 17497649]

16. Cam K, Yucel S, Turkeri L, et al. Accuracy of transrectal ultrasound guided prostate biopsy: histopathological correlation to matched prostatectomy specimens. *Int J Urol.* 2002; 9:257–260. [PubMed: 12060438]
17. Karakiewicz PI, Chun FK, Gallina A, et al. Biopsies performed at tertiary care centers are superior to referral biopsies in predicting pathologic Gleason sum. *J Endourol.* 2008; 22:533–538. [PubMed: 18355149]
18. Naughton CK, Miller DC, Mager DE, et al. A prospective randomized trial comparing 6 versus 12 prostate biopsy cores: impact on cancer detection. *J Urol.* 2000; 164:388–392. [PubMed: 10893592]
19. Emiliozzi P, Scarpone P, DePaula F, et al. The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. *J Urol.* 2004; 171:197–199. [PubMed: 14665875]

Figure 1.

The biochemical recurrence-free survival for men treated with radical prostatectomy was not different for men who had biopsy GS upgraded upon review at MD Anderson ($p=0.835$).

Figure 2.

The biochemical recurrence-free survival for men treated with brachytherapy was not different for men who had biopsy GS upgraded upon review at MD Anderson ($p=0.531$).

Table 1

Characteristics of men undergoing Radical Prostatectomy or Brachytherapy

	Radical Prostatectomy (n=279)	Brachytherapy (n=92)	
Mean age (years)	60.1	65.1	p <0.0001
Mean PSA level (ng/mL)	6.1	6.6	p=0.1177
<u>Clinical Stage</u>			p=0.5255
T1a	1 (0.4%)	0	
T1b	1 (0.4%)	0	
T1c	174 (62.4%)	65 (70.6%)	
T2a	80 (28.7%)	24 (26.1%)	
T2b	21 (7.5%)	3 (3.3%)	
T2c	2 (0.7%)	0	
* Biopsy GS			
6	185 (66.3%)	82 (89.1%)	p <0.0001
7	94 (33.7%)	10 (10.9%)	
GS 7 (3+4)	74	9	
GS 7 (4+3)	20	1	
Median follow-up time (years)	7.2	7.6	p=0.0959

Abbreviations: PSA, prostate-specific antigen; GS, Gleason score.

* GS refers to the Gleason score assigned after central pathologic review of biopsy specimens at MD Anderson.

Table 2

Pathology upgrading for men treated with Surgery or Brachytherapy

GS upgrading between specimens*:	Radical Prostatectomy (n=279)	Brachytherapy (n=92)
Diagnostic biopsy → Central pathologic review	34 (12.2%)	15 (16.3%)
Centrally reviewed biopsy → Radical Prostatectomy specimen	121 (43.4%)	N/A
<u>GS upgrading by number of biopsy cores:</u>	Centrally reviewed biopsy → Radical Prostatectomy specimen	
Sextant	65/128 (50.8%)	
Extended [10–12-core]	14/29 (48.3%)	
Other	42/122 (34.4%)	
Total	121/279 (43.4%)	
<u>Patients with GS upgrading:</u>		
Sextant	65/121 (53.7%)	
Extended [10–12-core]	14/121 (11.6%)	
Other	42/121 (34.7%)	

GS = Gleason Score

* p = 0.18 for testing whether Radical Prostatectomy (RP) and Brachytherapy (BT) have the same distribution of upgrading from diagnosis to central review